

Flat and Depressed Lesions of the Colon and Rectum: Pathogenesis and Clinical Management

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Abstract

Introduction: It is not clear whether flat lesions play a role in the pathogenesis of colorectal carcinoma. Flat lesions are being increasingly recognised with new colonoscopic techniques. **Materials and Methods:** A total of 10,939 consecutive colonoscopies were performed over a 9-year period. After bowel preparation with polyethylene glycol electrolyte lavage solution, high-resolution video colonoscopy and indigocarmine spraying were performed to detect flat lesions. All lesions suggesting neoplastic change were removed by polypectomy or surgery. Cancers invading beyond the submucosal layer were excluded from this analysis. The gross appearance of flat-type lesions was classified as flat elevated type or flat depressed type based on the presence or absence of central depression. **Results:** A total of 5408 neoplastic lesions were index lesions, including 5035 adenomas and 373 carcinomas (124 with submucosal invasion). The prevalence of flat depressed and flat elevated lesions were 2.8% and 18.1%, respectively. Submucosal invasion rates were 17.1% in the flat depressed, 0.8% in the flat elevated, 1.6% in the sessile, 4.0% in pedunculated lesions and 9.3% in creeping lesions. The submucosal invasion rate in the flat depressed lesions was significantly higher than in any others, except for creeping lesions ($P = 0.06$). The percentage of flat elevated and flat depressed carcinomas among all carcinomas invading the submucosa was 6.5% and 21.0%, respectively. **Conclusion:** Flat lesions were common during routine colonoscopy. One-quarter of colorectal cancers may be derived from flat lesions. Training in dye spray technique may result in a higher detection rate of flat colonic lesions.

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Key words: Carcinogenesis, Chromoscopy, Flat adenoma, High-resolution video endoscope

Introduction

It was previously thought that the vast majority of colorectal cancers were derived from polypoid adenomas.¹ However, several investigators²⁻⁶ have noted that most colorectal cancers which developed from flat or depressed neoplastic lesions remained undetectable by conventional colonoscopy. According to their reports, flat lesions, particularly depressed ones, demonstrate a higher incidence of carcinoma and possess a greater disposition to invade the submucosal layer than polypoid lesions. This would indicate that flat lesions play an important role in the pathogenesis of colorectal carcinoma.

Since 1992, we have performed meticulous chromo-colonoscopy to detect flat or depressed lesions. Consequently, we have identified a large series of flat and depressed lesions. In this paper, we assess the features of

flat and depressed lesions by analysing this series of colorectal lesions.

Materials and Methods

Colonoscopy and Index Lesions

Colorectal lesions detected on consecutive colonoscopy in Jichi Medical School Hospital, between January 1992 and June 2001, and in Miyashita Hospital, between April 1992 and May 1997, were enrolled into this study. All colonoscopies in both hospitals were performed according to the same protocol as follows. Using high-resolution video endoscopes, the authors performed meticulous colonoscopy after bowel preparation with 2L of polyethylene glycol electrolyte lavage solution.⁷ When flat and depressed lesions were suspected, an adequate amount of 0.2% indigocarmine solution was sprayed on the colonic

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surface to avoid overlooking minute flat and depressed lesions. All lesions suggesting neoplastic development were removed by polypectomy, including endoscopic mucosal resection. If the lesions could not be removed by colonoscopy, they were resected by surgical intervention. Since April 1997, however, sessile or flat elevated lesions measuring 5 mm or less, which were detected in surveillance colonoscopy after colorectal cancer surgery, were left untreated. These lesions were serially studied to investigate the natural history of small polyps, and were not included in this study. In addition, recurrent lesions following endoscopic resection and lesions detected in patients with both familial adenomatous polyposis and ulcerative colitis were excluded from this study.

Histological Examination and Index Lesions

We used a standard protocol to examine the resected specimens. Each lesion was fixed in formalin and sections were stained with haematoxylin and eosin. Adenomas, including serrated adenomas and carcinomas, confined to the mucosal or submucosal layer were analysed in this study. "Intramucosal carcinoma" was defined according to the criteria proposed by Rubio et al.^{8,9} Carcinomas invading beyond the submucosa, carcinoid tumours and non-neoplastic polyps, such as hyperplastic polyps, inflammatory polyps, Peuts-Jeghers polyps and juvenile polyps, were excluded.

Evaluation of Gross Appearance

The gross appearance was classified as the flat type, protruded type or creeping type^{10,11} based on both colonoscopic findings and the resected specimens, although colonoscopic findings were given priority over macroscopic appearance of the resected specimen. On colonoscopy, flat-top lesions were defined as flat, lesions with a hemispherical top as protruded and lesions with a multi-nodular appearance as creeping. When the lesions were resected by endoscopic mucosal resection, including the surrounding normal mucosa, we defined the height of the flat-type lesion as being less than twice that of the surrounding normal mucosa. Lesions showing exophytic growth or vertical extension were classified into protruded or creeping types. Flat lesions were further classified into flat elevated and flat depressed based on the presence or absence of central depression. Protruded-type lesions were further classified into sessile and pedunculated types based on the presence or absence of stalk.

Evaluation of Size

In cases of cold biopsy, hot biopsy and conventional snare polypectomy, the size was estimated using the open forceps technique prior to treatment. In cases of endoscopic mucosal resection and surgery, the lesion of the specimen

was measured after treatment.

Statistical Analysis

Statistical analysis was performed by chi-square tests. *P* values of less than 0.05 were considered as statistically significant.

Results

Selection of Lesions

Ten thousand, nine hundred and thirty-nine patients underwent colonoscopy, and 6278 colorectal lesions were detected. Of these, 5978 colorectal lesions were resected and examined histologically and 60 lesions were excluded by exclusion criteria. Histology of the remaining 5918 lesions were adenoma in 5037, carcinoma in 371, hyperplastic polyp in 286, inflammatory polyp in 56, carcinoid tumour in 6, other lesion in 16, normal mucosa in 136 and unknown histology in 10. In this study, both 5037 adenomas and 371 carcinomas, a total of 5408 lesions, were subjected to further analysis. Initial treatments of the lesions were cold biopsy in 368, hot biopsy in 2448, conventional snare polypectomy in 1634, endoscopic mucosal resection with saline injection in 831, local excision for rectal lesion in 21 and bowel resection in 106.

Site, Gross Appearance and Size

The site, gross appearance and size of the 5408 lesions are summarised in Table I. Flat lesions, including flat depressed and flat elevated, comprised approximately 20%.

TABLE I: CHARACTERISTICS OF THE LESIONS (n = 5408)

Variable	Case	(%)
Site		
Cecum	350	(6.5)
Ascending colon	1137	(21.0)
Transverse colon	1372	(25.4)
Descending colon	542	(10.0)
Sigmoid colon	1387	(25.6)
Rectum	620	(11.5)
Gross appearance		
Flat depressed	152	(2.8)
Flat elevated	977	(18.1)
Sessile	3725	(68.9)
Pedunculated	403	(7.5)
Creeping	151	(2.8)
Size		
5 mm or less	3451	(63.8)
6 - 10 mm	1359	(25.1)
11 - 15 mm	288	(5.3)
16 - 20 mm	168	(3.1)
21 mm or larger	142	(2.6)

TABLE II: SITE AND GROSS APPEARANCE IN ALL NEOPLASTIC LESIONS

Site	Gross appearance of neoplastic lesions									
	Flat depressed		Flat elevated		Sessile		Pedunculated		Creeping	
	Case	(%)	Case	(%)	Case	(%)	Case	(%)	Case	(%)
Cecum	1	(0.7)	48	(4.9)	265	(7.1)	5	(1.2)	31	(20.5)
Ascending colon	22	(14.5)	140	(14.3)	868	(23.3)	76	(18.9)	31	(20.5)
Transverse colon	58	(38.2)	342	(35.0)	885	(23.8)	68	(16.9)	19	(12.6)
Descending colon	14	(9.2)	155	(15.9)	337	(9.0)	34	(8.4)	2	(1.3)
Sigmoid colon	45	(29.6)	233	(23.8)	894	(24.0)	194	(48.1)	21	(13.9)
Rectum	12	(7.9)	59	(6.0)	476	(12.8)	26	(6.5)	47	(31.1)
Total	152	(100.0)	977	(100.0)	3725	(100.0)	403	(100.0)	151	(100.0)

TABLE III: SITE AND GROSS APPEARANCE IN CANCERS

Site	Gross appearance of cancers									
	Flat depressed		Flat elevated		Sessile		Pedunculated		Creeping	
	Case	(%)	Case	(%)	Case	(%)	Case	(%)	Case	(%)
Cecum	1	(2.6)	1	(2.8)	6	(3.4)	0	(0.0)	7	(13.5)
Ascending colon	11	(28.2)	8	(22.2)	15	(8.6)	6	(8.3)	6	(11.5)
Transverse colon	9	(23.1)	5	(13.9)	12	(6.9)	7	(9.7)	5	(9.6)
Descending colon	1	(2.6)	1	(2.8)	8	(4.6)	3	(4.2)	1	(1.9)
Sigmoid colon	10	(25.6)	11	(30.6)	65	(37.4)	50	(69.4)	7	(13.5)
Rectum	7	(17.9)	10	(27.8)	68	(39.1)	6	(8.3)	26	(50.0)
Total	39	(100.0)	36	(100.0)	174	(100.0)	72	(100.0)	52	(100.0)

Relationship between Site and Gross Appearance

The relationship between site and gross appearance is shown in Table II. The distribution of flat depressed lesions was similar to that of flat elevated ones. In the transverse colon, the percentage of both flat elevated and flat depressed lesions was higher than that of sessile ones ($P < 0.0001$). When the distribution of the carcinomas, including mucosal

carcinomas and submucosal carcinomas, was analysed (Table III), the prevalence of flat cancers in the right-sided colon was significantly higher than that of protruded and creeping cancers ($P < 0.0001$).

Relationship between Histology and Gross Appearance

The relationship between histology and gross appearance

TABLE IV: HISTOLOGY AND GROSS APPEARANCE

Gross appearance	Adenoma		m-carcinoma		sm-carcinoma		Total	
	Case	(%)	Case	(%)	Case	(%)	Case	(%)
Flat depressed	113	(74.3)	13	(8.6)	26	(17.1)	152	(100)
Flat elevated	941	(96.3)	28	(2.9)	8	(0.8)	977	(100)
Sessile	3551	(95.3)	114	(3.1)	60	(1.6)	3725	(100)
Pedunculated	331	(82.1)	56	(13.9)	16	(4.0)	403	(100)
Creeping	99	(65.6)	38	(25.2)	14	(9.3)	151	(100)
Total	5035	(93.1)	249	(4.6)	124	(2.3)	5408	(100)
Flat depressed	113	(2.2)	13	(5.2)	26	(21.0)	152	(2.8)
Flat elevated	941	(18.7)	28	(11.2)	8	(6.5)	977	(18.1)
Sessile	3551	(70.5)	114	(45.8)	60	(48.4)	3725	(68.9)
Pedunculated	331	(6.6)	56	(22.5)	16	(12.9)	403	(7.5)
Creeping	99	(2.0)	38	(15.3)	14	(11.3)	151	(2.8)
Total	5035	(100)	249	(100)	124	(100)	5408	(100)

m-carcinoma: carcinoma confined to the mucosal layer; sm-carcinoma: carcinoma confined to the submucosal layer

is shown in Table IV. Malignancy rates, including mucosal carcinoma and submucosal carcinoma, of both the flat depressed type and creeping type were significantly higher than those of lesions with any other gross appearance ($P < 0.05$). The rate of submucosal cancer in the flat depressed type was significantly higher than those in the flat elevated type, the sessile type and pedunculated type ($P < 0.0001$), and there was a possible difference between the flat depressed type and creeping type ($P = 0.06$). In submucosal carcinomas, the percentage of flat depressed and flat elevated lesions was 21.0% and 6.5%, respectively. Flat lesions occupied 27.5% of all submucosal carcinomas.

Relationship among Histology, Gross Appearance and Size

The relationship among malignancy rate, gross

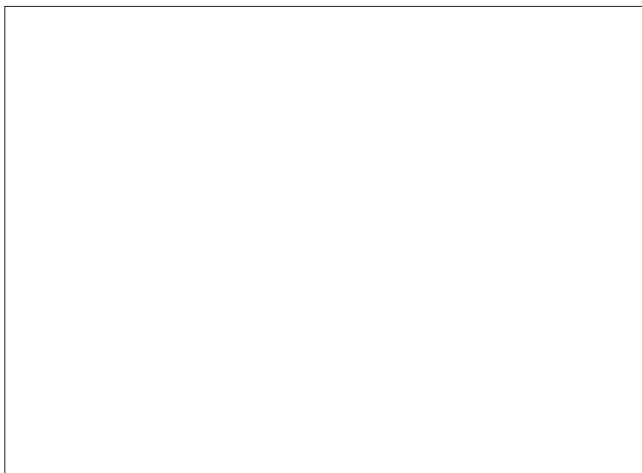


Fig. 1. Percentage of both mucosal carcinoma and submucosal carcinoma is shown in Figure 1. The malignancy rate of the flat depressed type lesion was the highest in every size category. The malignancy rates of flat depressed type in “6-10 mm” and “11-15 mm” were significantly higher than those of other gross appearances ($P < 0.01$).

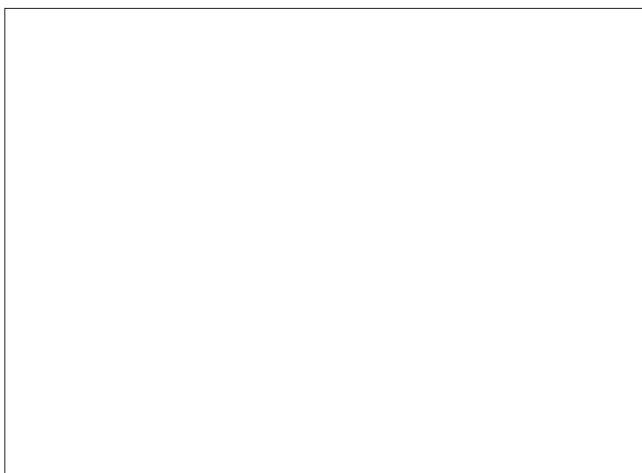


Fig. 2. Percentage of submucosal carcinoma is shown in Table II. Except for the size category “5mm or less”, the submucosal carcinoma rate in the flat depressed type was the highest in each size categories. The differences were significant and were especially remarkable in both “11-15 mm” and “15-20 mm” ($P < 0.001$).

appearance and size is shown in Figure 1. The malignancy rate of the flat depressed type lesion was the highest in every size category. In “5mm or less”, the malignancy rate of the flat depressed type lesion was significantly higher than that of the flat elevated type or sessile type ($P < 0.05$). The malignancy rates of flat depressed type in “6-10 mm” and “11-15 mm” were significantly higher than those of other gross appearances ($P < 0.01$). In the size category “16-20 mm”, the malignancy rate of the flat depressed type lesion was significantly higher than others, except for the sessile type ($P < 0.05$).

The relationship among submucosal carcinoma rate, gross appearance and size is shown in Figure 2. There was only 1 submucosal carcinoma measuring 5 mm or less. Except for the size category “5 mm or less”, submucosal carcinoma rate in the flat depressed type was the highest in each size categories. The differences were significant and were especially remarkable in both “11-15 mm” and “15-20 mm” ($P < 0.001$).

Case Presentation

Case 1 (Figs. 3a & 3b): This lesion was detected in a 60-year-old male who underwent surveillance colonoscopy after post-polypectomy. Colonoscopy revealed that the lesion was 12 mm in size and showed slightly reddish and minutely rough surface. On plain view, the depressed area of the lesion was unclear. On spraying indigocarmine solution, the margin of the lesion and the depressed area were visualised clearly. Based on these findings, this lesion was diagnosed to be cancer with massive submucosal invasion. The histology was consistent with the colonoscopic diagnosis.

Case 2 (Figs. 4a & 4b): This lesion was detected in a 62-year-old male who underwent surveillance colonoscopy after colorectal cancer surgery. On plain colonoscopic view, the lesion was 12 mm in size and showed slightly reddish and smooth surface. Spraying with indigocarmine solution visualised the margin of the lesion clearly, and it clarified that the lesion had neither a rough surface nor apparent depression. Histologically, this lesion was tubular adenoma with mild dysplasia.

Discussion

Definition of Flat Lesions

A clear definition of flat lesions is crucial to investigate their actual prevalence and nature. However, the gross appearance of all lesions cannot be precisely evaluated from resected specimens. This is because not all specimens include the surrounding normal mucosa. Accordingly, any evaluation of the gross appearance is dependent on the colonoscopic findings. Muto et al,² who first described flat adenoma, did not propose a clear definition of flat adenoma,

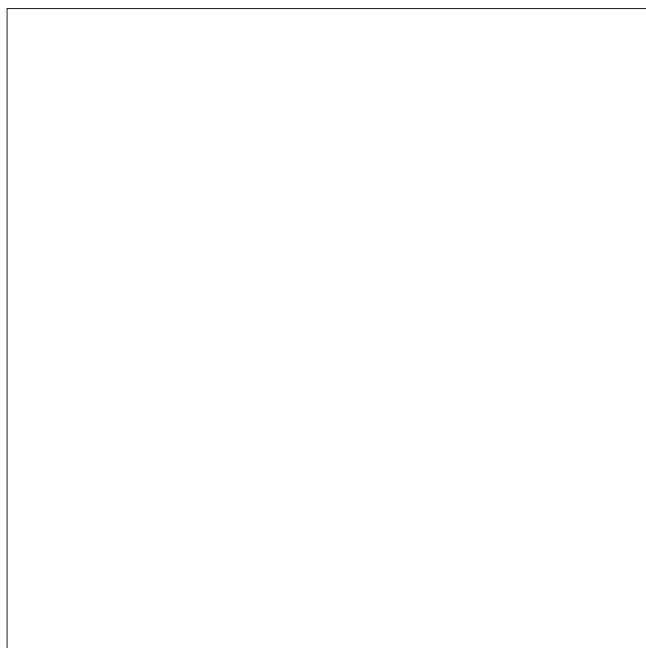


Fig. 3a. On plain colonoscopic view, the lesion was 12 mm in size and showed a slightly reddish and minutely rough surface. The depressed area of the lesion was not clear.

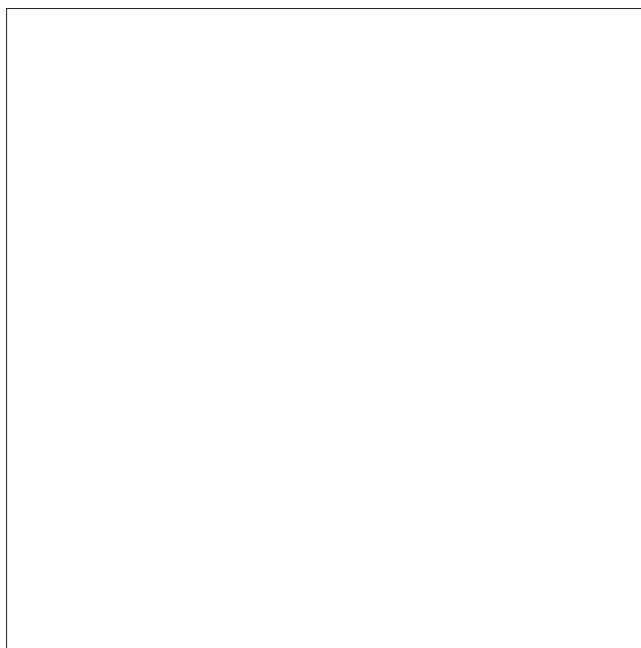


Fig. 3b. On spraying the indigocarmine solution, the margin of the lesion and the depressed area were visualized clearly. The lesion was diagnosed to be cancer with massive submucosal invasion.

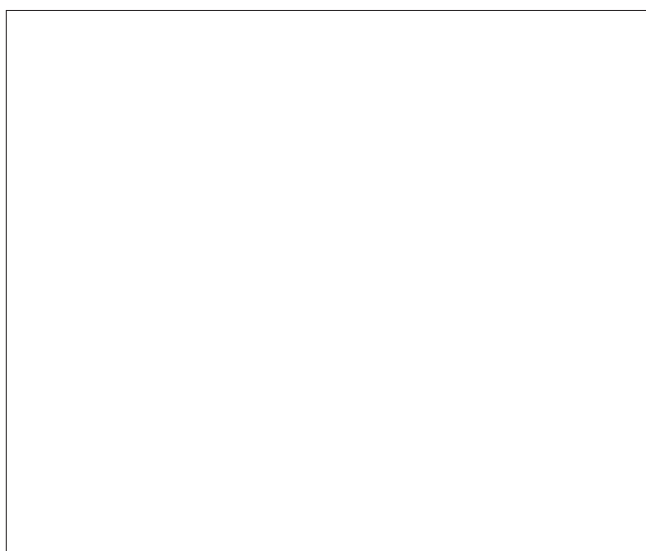


Fig. 4a. On plain colonoscopic view, the lesion was 12 mm in size and showed a slightly reddish and smooth surface.

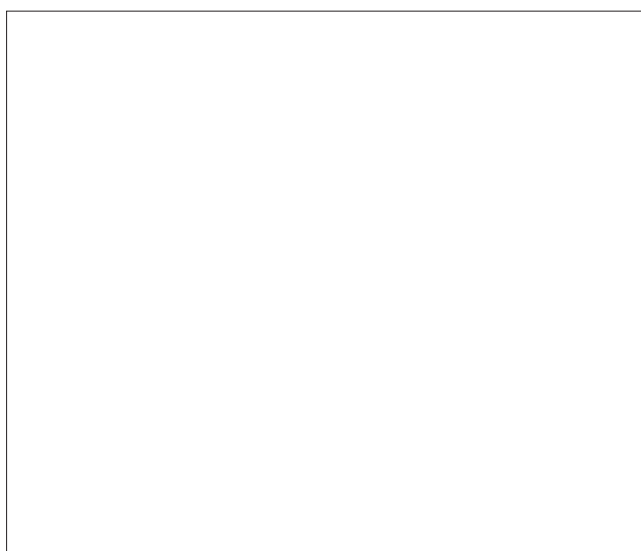


Fig. 4b. Spraying of the indigocarmine solution visualised the margin of the lesion clearly and clarified that the lesion had neither a rough surface nor an apparent depression.

but rather described its characteristic features: slight elevations with a reddish surface and a height less than twice the thickness of the surrounding normal mucosa on histology. Kuramoto and Oohara³ proposed that the height of flat early cancer did not exceed 50% of the longer diameter. This proposal is generally not accepted. Wolber and Owen⁴ advocated a strict definition comprising three points:

1) flat lesions lack exophytic polypoid configuration;

histologically, the dysplastic mucosa is never greater than two times the thickness of the adjacent non-dysplastic mucosal segment;

2) flat lesions show radial extension of the dysplastic epithelium in the superficial luminal portion of the mucosa without vertical extension; and

3) all colonoscopically excised lesions are not clinically described as pedunculated or exophytic.

At present, their definition has almost been accepted by Japanese^{12,13} and Western investigators.^{14,15} Furthermore, Shimoda et al¹⁶ paid special attention to the intramucosal growth pattern. They reported that some protruded lesions originated from flat lesions because of the remnant of a flat mucosal lesion in the marginal area. Considering the above literature, we proposed a strict definition of flat lesions, which is described in the Materials and Methods section of the present paper. It is similar to that by Wolber and Owen,⁴ and would be acceptable to many gastroenterologists.

Clinical Importance of Flat Depressed Lesions

From the outset, “flat adenoma” was used to describe both flat depressed and flat elevated lesions.²⁻⁴ Therefore, flat elevated lesions were frequently confused with flat depressed ones. When both lesions were classified as “flat adenoma”, flat lesions were generally considered to have a high malignancy rate. In fact, the malignancy rate of flat elevated lesions is not higher than that of sessile lesions, and flat depressed lesions alone show a significantly higher malignancy rate in our data. These results are consistent with related reports.^{6,17,18} This suggests that the biological behaviour of flat depressed lesions may be quite different from that of flat elevated ones. Therefore, flat depressed lesions should be distinguished from flat elevated lesions in practice, although they resemble flat elevated lesions in colonoscopic appearance when dye spraying is not applied.

Incidence of Flat Depressed Lesions

Flat elevated lesions can be frequently detected in general practice, while flat depressed lesions are not so common. In our series, the percentage of flat elevated lesions in all neoplastic lesions was 18% and that of flat depressed lesions was 2.8%. Kudo and Kashida,¹⁸ who detected a large series of flat depressed lesions, reported that the percentage of flat elevated and flat depressed lesions was 36% and 4.5%, respectively. In a Western population, Jaramillo et al¹⁷ reported an incidence of flat lesions using high-resolution video endoscopy and chromoscopy. According to them, the percentage of flat elevated and flat depressed lesions in all detected neoplastic lesions was 37% and 5.4%, respectively. Although there are small differences because of the different populations, these data suggest that flat depressed lesions are not unusual in general practice, and that colonoscopists cannot neglect flat lesions, especially those with a depressed appearance. Regarding the site of flat lesions, our series showed a high prevalence in the transverse colon. Jaramillo et al¹⁷ have reported an almost similar distribution. Mitooka et al,¹³ who described 37 flat depressed neoplastic lesions, showed 68% were located in the transverse colon. This might be attributed to the fact that flat depressed lesions have a tendency to develop in the transverse colon.

Detection of Flat Depressed Lesions

Flat depressed lesions can be detected by a slightly reddish or pale appearance on plain endoscopy.^{2,3,5,6,13-15,17,18} Therefore, the detection and resection of small flat depressed lesions require special procedures, which are frequently performed in Japan. They consist of the use of high-resolution video endoscopy, dye spray with indigocarmine solution and meticulous observation. From our experience, polyethylene glycol lavage electrolyte solution is ideal for clearing faeces, although compliance is not excellent compared with sodium phosphate solution and magnesium citrate solution.^{19,20} Recently, high-resolution video endoscopy has become prevalent around the world, and there are several reports^{13,17} advocating its efficacy in detecting small flat lesions. It is indispensable in harvesting an abundance of small flat lesions. The indigocarmine spraying technique^{13,17,21} is also indispensable, although methylene blue has frequently been used in the beginning.^{2,3,5} Indigocarmine is a non-absorbable dye and it does not stain the colonic mucosa. When the indigocarmine solution is sprayed, the dye will accumulate within the mucosal sulcus to provide a clear visualisation of the small depressed lesions. The technique can be repeated if enhancement is not effective. In our series, many small depressed lesions could be detected using the polyethylene glycol electrolyte lavage solution, high-resolution video endoscopy and indigocarmine spraying technique. Recent reports^{14,15,22} showed evidence that these procedures are very useful for detecting small flat and depressed lesions.

Do the Majority of Colorectal Cancers Originate from Flat Adenomas?

Morson²³ has estimated that up to two-thirds of all colorectal carcinomas arise from polypoid adenomas, but was unable to explain the origin of the remainder. National Polyp Study²⁴ states that excision of polypoid adenomas would have failed to prevent up to 24% of all subsequent carcinomas. These suggest that the remaining colorectal cancer might have originated from flat adenomas. According to our data on submucosally invasive cancers, approximately 28% showed a flat appearance. Kudo and Kashida¹⁸ also reported a similar distribution of the two different types of lesions in gross appearance. Therefore, it can be considered that three-quarters of colorectal cancers originate from polypoid-type lesions and one-quarter from flat lesions. Conventional colonoscopy which targets the polypoid lesions, would not be sufficient to detect other colorectal cancers in the early stages.

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